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# SCIENCE AND TECHNOLOGY FOR DISEASE CONTROL:

# PAST, PRESENT AND FUTURE

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*"Medicine may be on the brink of one of the greatest transformations in its long and chequered history. But right now, after the golden age of some generations back, the public climate is not one of optimism but of new-millenial anxiety."*

Roy Porter, British Historian, 2002

As we have move into the new millennium it is becoming increasingly clear that the biomedical sciences are entering the most exciting phase of their development. Yet, paradoxically, medical practice is passing through a phase of increasing uncertainty, both in advanced industrial countries and the developing world. None of the richer countries have been able to solve the problem of the spiralling costs of health care consequent on technological development, public expectations, and, in particular, the rapidly increasing size of their elderly populations. On the other hand, the people of many developing countries are still living in dire poverty with dysfunctional healthcare systems and extremely limited access to basic medical healthcare.

It is against this complex background that this chapter examines the role of science and technology for disease control in the past and present, and attempts to assess the potential of the remarkable developments in the basic biomedical sciences for global healthcare in the future.

**HISTORICAL INTRODUCTION**

From the earliest documentary evidence that has survived from the ancient civilisations of Babylonia, Egypt, China and India, it is clear, not surprisingly, that longevity, disease and death are among humanity's oldest preoccupations. But from ancient times to the Renaissance knowledge of the living world changed very little, the distinction between animate and inanimate objects was blurred, and speculations about living things were based on prevailing ideas about the nature of matter.

Advances in science and philosophy throughout the 16$^{th}$ and 17$^{th}$ Centuries led to equally momentus changes in medical sciences. The elegant anatomical

dissections of Vesalius swept away centuries of misconceptions about the relationship between structure and function of the human body, the work of Newton, Boyle, and Hooke disposed of the basic Aristotelian elements of earth, air, fire and water, and Hooke, through his development of the microscope, showed that there was a hitherto invisible world to explore. In 1628 William Harvey described the circulation of the blood, a discovery which, because it was based on careful experiments and measurement, signalled the beginnings of modern scientific medicine.

After steady progress during the 18th Century the biological and medical sciences began to advance at a remarkable rate during the 19th Century, which saw the genuine beginnings of modern scientific medicine. Charles Darwin changed the whole course of biological thinking and Mendel laid the ground for the new science of genetics which was used later to describe how Darwinian evolution came about. Pasteur and Koch founded modern microbiology and Bernard and his followers enunciated the seminal principle of the constancy of the internal environment of body, a notion that profoundly influenced the development of physiology and biochemistry. And with the birth of cell theory modern pathology was established.

These advances in the biological sciences were accompanied by practical developments at the bedside. These included the invention of the stethoscope and an instrument for measuring blood pressure, the first use of X-rays, the development of anaesthesia, and early attempts at the classification and a more humane approach to management of psychiatric disease.

The 19th Century also saw the early development of the use of statistics for analysing data obtained in medical practice and the slow evolution of public health and preventive medicine.

Significant advances in public health occurred on both sides of the Atlantic. After the cholera epidemics of the mid-19th Century public health boards were established in many European and American cities. The Public Health Act, passed in the UK in

1848, made provision for the improvement of streets, construction of drains and sewers, collection of refuse and the procurement of clean domestic water supplies. And, equally importantly, the first attempts were made to record basic health statistics. For example, the first recorded figures for the USA showed that life expectancy at birth for those who lived in Massachusetts in 1870 was 43 years; the number of deaths per 1,000 live births in the same population was 188. At the same time, because it was becoming increasingly clear that communicable diseases were greatly depleting the workforce required to generate the potential rewards of colonialisation, considerable efforts were channelled into controlling infectious diseases in many countries that had come under colonial domination, particularly hookworm and malaria.

There is no doubt, however, that until the 19th Century curative medical technology made little impact on the health of society, and many of the improvements over the centuries resulted from higher standards of living, improved nutrition, better hygiene and other modifications of the environment. But the ground was laid for a dramatic change in this picture during the second half of the 20th Century, although there is still considerable controversy about how much we owe to the impact of scientific medicine and how much to continued improvements in our environment (Porter, 1997).

This balance between the potentials of the basic biological sciences compared with more simple public health measures for determining the health of our societies, both in the developed and developing countries, remains controversial and is one of the major issues to be faced by those who plan the development of healthcare services for the future.

## SCIENCE, TECHNOLOGY AND MEDICINE IN THE 20TH CENTURY

Although possibly because of the debilitating effect of two major world wars, progress in the medical sciences was rather slow during the first half of the 20th Century, the position changed quite dramatically after the Second World War, a period which many still believe was the period of major achievement in the biomedical sciences and in the improvement of the health of society. In this section we will outline some of these developments and the effect that they have had on medical practice, both in the developed and developing countries. More extensive treatments of this topic are available in several monographs (Weatherall 1995; Porter 1997; Cooter and Pickstone, 2000).

### Epidemiology and Public Health

Modern epidemiology came into its own after the Second World War when it was first applied to the study of non-infectious disease using increasingly sophisticated statistical methods to analyse the patterns and associations of diseases in large populations. There is no doubt that the emergence of clinical epidemiology marked one of the most important successes of the medical sciences of the 20th Century.

Up to the 1950's conditions such as heart attacks, stroke, cancer, diabetes and many others were bundled together as degenerative disorders, implying that they might be the natural result of wear and tear and the inevitable consequence of ageing. However, information about their frequency and distribution and, in particular, the speed in which their frequency increased in association with environmental change, provided excellent evidence that many of them have a major environmental component. For example, death certificate rates for cancers of the stomach and lung rose so sharply between 1950 and 1973 that there must have been major environmental factors at work generating these diseases in different populations.

The first major success of clinical epidemiology was the demonstration of the relationship between cigarette smoking and lung cancer by Austin Bradford Hill and

Richard Doll in the UK. This work was later replicated in many studies; currently it is estimated that tobacco causes about 8.8% of deaths (4.9 million) and 4.1% of Dalys (59.1 million) (WHO, 2002). Despite this information the tobacco epidemic continues, with at least 1 million more deaths attributable to tobacco in 2000 compared with 1990, mainly in the developing countries.

The application of epidemiological approaches of this kind to the study of large populations over a long period has provided further invaluable information about environmental factors and disease. One of the most thorough, involving the follow-up of over 50,000 males in Framingham, Massachusetts, showed quite unequivocally that a number of factors seem to be linked with the likelihood of developing heart disease. Work of this type led to the concept of 'risk factors' among them being smoking, diet, especially the intake of animal fats, blood cholesterol levels, obesity, lack of exercise, and raised blood pressure. The appreciation by epidemiologists that focusing attention on interventions against low risk factors that involve large numbers of people, as opposed to focusing on the small numbers of subjects at high risk, was an important advance. And later it led to the definition of how important environmental agents may interact one with another, the increased risk of death from tuberculosis in smokers in India for example.

A vast amount of work has gone into identifying risk factors for other diseases, hypertension, obesity and its accompaniments, and other forms of cancer, for example. Risk factors defined in this way, and from similar analyses of the pathological role of environmental agents such as unsafe water, poor sanitation and hygiene, pollution, and others, form the basis of the WHO's 2002 Report, which sets out a programme for controlling disease globally by the reduction of 10 of them: underweight; unsafe sex; high blood pressure; tobacco consumption; alcohol consumption; unsafe water; sanitation and hygiene; iron deficiency; indoor smoke from solid fuels; high cholesterol; and obesity. It is calculated that these account for more than one third of all deaths worldwide.

There have been some downsides to the epidemiological approach however. Where, as it seems likely, risk factors are heterogeneous or of only limited importance even studies involving large populations continue to give equivocal or contradictory results. Furthermore, there is still a major lack of understanding, not just on the part of the general public but also on those who administer health services, about the precise meaning and interpretation of 'risk'. A great deal of education is still required in this respect. And the confusing messages coming from this field have led to a certain amount of public cynicism about risk factors, thus diminishing the impact of information about those which have been established on a solid basis. Furthermore, a great deal of work is required on the psychological aspects of the public perception of risk factors. It is still not clear why so many people in the developed countries ignore those which are based on solid data; much remains to be learnt about the social, cultural, psychological, and ethnic differences with respect to education about important risk factors for disease. And, as pointed out in a recent WHO Report, very little work has been done regarding the perception of risk factors in the developing countries (WHO, 2002).

A more recent development in the field of clinical epidemiology, and one which may have major implications for the developing countries, stems from the work of Barker and his colleagues, who obtained evidence suggesting that death rates from cardiovascular disease fell progressively with increasing weight, head circumference, and other measures of increased development at birth (Barker 2001). Further work has suggested that the development of obesity, and type 2 diabetes, which forms part of the metabolic syndrome, are also associated with low birth weight. The notion that early fetal development may have important consequences for disease in later life is still under evaluation but its implications, particularly for the developing countries, may be far reaching.

The other major development which arose from the application of statistics to medical research was the development of the randomised control trial (RCT). The principles of numerically based experimental design was set out in the 1920's by the

geneticist Ronald Fisher and applied with increasing success after the Second World War, starting with the work of Bradford Hill, Doll and Cochrane. Various variations on this theme have become central to every aspect of clinical research involving the assessment of different forms of treatment. More recently this approach has been extended to provide broad-scale research syntheses to help to inform healthcare and research. By increasing the numbers of patients involved in trials, together with the development of meta-analysis and electronic technology for updating results, it has been possible to provide broad-scale analyses, combining the results of many different trials. While meta-analysis has its problems, notably the lack of publication of negative trial data, and there are many potential sources of bias in the reporting of clinical trials, these difficulties are gradually being addressed (Egger *et al*, 2001).

The Cochrane Collaboration was established in 1993 and its work involves preparing, maintaining and disseminating syntheses of reliable research evidence on the effects of interventions for prevention, treatment and rehabilitation in healthcare. Thousands of people from over 70 countries contribute to the work of the collaboration, and this development and similar bodies are helping to improve the standards of the research-trial review process. The Collaboration includes clinical scientists from both the developed and developing countries (Chalmers 1993).

The other more recent development in the fields of epidemiology and clinical trials come under the general heading of Evidence-Based Medicine (EBM) (Sackett *et al*, 1996). Although it is self-evident that the medical profession should base its work on the best available evidence, and there is nothing very new about this notion, the rise of EBM as a way of thinking has been a valuable addition to the development of good clinical practice over the years. It is, in fact, a way of thinking which covers certain skills which are not always self-evident, including finding and appraising evidence, developing the capacity of individual organisations to use evidence, and particularly, implementation, that is actually getting research into practice. Its principles are equally germane to the developed and developing countries, and the skills required, particularly numerical, will have to become part of the education of

physicians of the future. To this end, the EBM Toolbox has been established (Website: http://www.ish.ox.ac.uk/ebh.html). In this context it should be remembered, however, that evidence for 'best practice' obtained from large clinical trials may not always be applicable to particular patients; obtaining a balance between better EBM and the kind of individualised patient care which forms the basis for good clinical practice will be a major challenge for medical education in the future.

**The partial control of infectious disease**

The control of communicable disease has been the major advance in scientific medicine of the 20th Century. It reflects the combination of improved environmental conditions and public health together with the development of immunisation, antimicrobial chemotherapy, and the increasing facility for the identity of new pathogenic organisms. Currently, live or killed viral or bacterial vaccines, or those based on bacterial polysaccharides or bacterial toxoids are licensed for the control of 29 common communicable diseases worldwide. The highlight of the field was the eradication of smallpox by 1977. The WHO's next target is the global eradication of poliomyelitis; between 1998 and 1999 the number of reported cases fell dramatically and only three major loci of transmission remained.

The Expanded Programme of Immunisation (EPI), launched in 1974, which with slight modification has been taken up by many countries, includes BCG and oral polio vaccine at birth, diphtheria, tetanus and pertussis at six, 10 and 14 weeks, and measles and, where relevant, yellow fever at nine months. Hepatitis B is added at different times in different communities. By 1998 hepatitis B vaccine had been incorporated into the national programmes of 90 countries but it is estimated that 70% of the world's hepatitis B carriers are still living in countries without programmes (Nossal 1999). Indeed, among 12 million childhood deaths analysed in 1998, close to four million were the result of diseases for which adequate vaccines are available.

The development of sulphonamides and penicillin in the period running up to the beginning of the Second World War was followed by a remarkable period of progress in the discovery of antimicrobial agents effective against bacteria fungi viruses, protozoa, and helminths. Overall, knowledge of the pharmacological mode of action of these agents is best established for antibacterial and antiviral drugs. Antibacterial agents may affect cell wall or protein synthesis, nucleic acid formation, or may act on critical metabolic pathways. Since viruses live and replicate in host cells, antiviral chemotherapy has presented a much greater challenge. But, particularly with the challenge posed by HIV/AIDS, a wide range of antiviral agents has been developed, most of which are either nucleoside analogues, nucleoside or non-nucleoside reverse-transcriptase inhibitors, or protease inhibitors. Essentially, these agents interfere with critical self-copying or assembly function of viruses or retroviruses. Similarly, there is increasing knowledge of the modes of action of antifungal and antiparasitic agents.

Resistance to antimicrobial agents has been recognised since the introduction of effective antibiotics; within a few years pencillin-resistant strains of *Staphylococcus aureus* became widespread and penicillin-sensitive strains are now very uncommon (Finch and Williams, 1999). Resistant strains of Gram-negative bacteria are now commonly found in high-dependency units (critical care), where they may cause epidemics. The international emergence of multi-resistant organisms, including multiple-antibiotic-resistant coagulase-negative staphylococci, has led to the rapid increase in the use of vancomycin. Vancomycin-resistant enterococci have also emerged, particularly in specialised facilities in hospitals, and leave few therapeutic options. Furthermore, there is a rapid increase in multiple drug-resistant infections caused by *Salmonella* spp and *Microbacterial tuberculosis*. At least in part, the problem of antibiotic resistance has been increased by indiscriminant and uncritical use of antibiotics in both medical practice and animal husbandry.

Resistance to antiviral agents is also becoming widespread (Perrin and Telenti, 1998). Recent data from the USA indicate that the number of patients newly

infected with HIV who carried a drug resistant virus had increased from 3.4% in 1995/98 to 12.4% in 1999/2000. Similar data from Europe show that 10% of newly infected Europeans carry a strain which is resistant to medication. Less is known about the position in the developing countries although almost certainly drug resistant strains will be emerging.

The position for malaria is equally worrying (Noedl *et al*, 2003). Chloroquine resistance is now widespread and quinine resistance has been encountered in parts of Southeast Asia. Similarly, mefloquine resistance has been reported in Africa, Southeast Asia and South America and multi-resistant strains of malarial parasites are being encountered. For example, the pyrimethamine-sulphonamide combination, at one time so valuable for the treatment of severe, quinine-resistant infections, is now ineffective in many parts of Asia, Latin America and Africa. While some of these findings require further verification, and it is possible that some forms of "resistance" reflect the ways in which drugs are compounded, there is no doubt that genuine drug-resistance is an increasingly serious problem for the malaria field.

In summary, while the 20$^{th}$ Century witnessed remarkable advances in the control of communicable disease the current position is uncertain. The emergence of new infectious agents, as witnessed by the SARS epidemic in 2002, is a reminder of the constant danger posed by the appearance of novel organisms; more than 30 new infective agents have been identified since 1970. Effective vaccines have not yet been developed for some of the commonest infections, notably tuberculosis, malaria and HIV, and there are rapidly increasing populations of organisms which are resistant to antibacterial and antiviral agents. Furthermore, there has been a decline in the development of new antibiotics and effective antiviral agents with which to control them. The indiscriminant use of antibiotics both in the community and in the hospital populations of the richer countries has encouraged their emergence, a phenomenon which has been exacerbated in some of the developing countries by the use of single antimicrobial agents when combinations would have been less likely to produce resistant strains. And public health measures have been hampered

by the rapid movement of populations and by war, famine, and similar social disruptions in the developing countries.

In short, the war against communicable disease is far from over and seems likely always to be with us.

**Pathogenesis, control and management of non-communicable disease**

The second half of the 20th Century has also seen major advances in the understanding of the pathophysiology and in the management of many common non-communicable diseases. It has been a phase of development of the medical sciences characterised by a remarkable increase in the acquisition of knowledge about the biochemical and physiological basis of disease, information that, combined with some remarkable developments in the pharmaceutical industry, has led to a situation in which there are few non-communicable diseases for which there is no treatment and many which, although not curable, can be controlled over long periods of time.

There seems little doubt that many of these advances have stemmed from medical research rather than improved environmental conditions. In 1980 Beeson published an analysis of the changes that occurred in the management of important diseases between the years 1927 and 1975, based on a comparison of methods for the treatment of these conditions in the first and 14th Editions of a leading American textbook of medicine. He found that, of 181 conditions for which there had been little effective prevention or treatment in 1927, at least 50 had been managed satisfactorily by 1975. Furthermore, most of these advances seem to have stemmed from the fruits of basic and clinical research directed at the understanding of disease mechanisms (Beeson 1980).

The pattern of development of modern cardiology is an excellent example of the way in which modern, high technology, 'patch-up', medicine has evolved. Indeed, this is one of the few areas of modern medicine in which there has been an adequate study of the origins of its successes. In 1976 Comroe and Dripps attained a consensus

from 140 cardiologists about the top 10 clinical advances in cardiovascular and chest medicine and surgery in the preceding 30 years. They then analysed the goals of the authors of the 529 key scientific papers that they believed had led to these achievements. Their analyses asked, specifically, whether they key research contained in these papers was 'basic' – that is not directed at a particular clinical question – or whether it was set out with the express objective of tackling a particular medical problem. Remarkably, they found that only 60% of the seminal work that formed the basis for modern cardiology was clinically directed, and that the remainder was in the basic sciences and had not been carried out with any particular clinical end in view (Comroe and Dripps, 1976).

The major technical advances which have led to a better appreciation of the physiology and pathology of the heart and circulation include studies of its electrical activity by electrocardiography, the ability to catheterise both sides of the heart, the development of echocardiography and, more recently, the development of sophisticated ways of visualising the heart by computerised axial tomography, nuclear magnetic resonance, and isotope scanning. The use of these valuable tools, both in health and disease, has led to a much better understanding of the physiology of the failing heart, and to the effects of coronary artery disease. The availability of these different imaging techniques combined with catheterisation has revolutionised the management of congenital heart disease. And a better understanding of the pathophysiology of cardiac disease and hypertension has provided a platform for major pharmaceutical advances in their management.

In the second half of the 20$^{th}$ Century a variety of extremely powerful and effective drugs were developed for the management of heart disease, including diuretics, beta blockers, a wide variety of anti-hypertensive agents, calcium channel blockers, and others. In addition, a powerful armamentarium of drugs which interfere with blood clotting was introduced and the role of 'old' agents like aspirin was assessed for the management of heart disease by information obtained from large clinical trials.

These developments have been accompanied by remarkable improvements in anaesthesia and in the surgical treatment of cardiac disease as well as congenital heart disease. By the late 1960's techniques were developed to bypass obstruction to the coronary arteries. Coronary bypass surgery became a major tool; by the earlyl 1980's approximately 100,000 patients were undergoing this procedure in the United States each year. There was also progress in treatment of heart disease resulting from abnormalities of cardiac rhythm, both pharmacologically and by the implantation of artificial pacemakers. More recently, the development of micro-electronic circuits has made it possible to construct implantable pacemakers. Following the success of renal transplantation, cardiac transplantation, and later heart and lung transplantation, became feasible and the results improved so rapidly that these procedures also became part of day to day clinical practice.

Much of this work has been backed up by large-scale controlled clinical trials. Studies of this kind made it absolutely clear that the early use of clot-dissolving drugs together with aspirin had a major effect on reducing the likelihood of recurrences after an episode of myocardial infarction. The large number of trials and observational studies of the effects of coronary bypass surgery and dilatation of the coronary arteries with balloons have given somewhat mixed results, although, overall, there seems little doubt that at least in some forms of coronary artery disease surgery is able to reduce pain from angina and, probably, prolong life. Similar positive results have been obtained in trials set out to evaluate the effect of the control of hypertension.

The management of other chronic diseases, notably those of the gastrointestinal tract, lung, and blood have followed along similar lines. Advances in our understanding of their pathophysiology, combined with advances in their analysis at the structural and biochemical levels have enabled many of them to be managed much more effectively. Again, the pharmaceutical industry has helped enormously by the development of agents such as the H2-receptor antagonists and a wide range of drugs directed at bronchospasm. And along the way there have been some

surprises; the discovery that peptic ulceration is almost certainly due to a bacterial agent has transformed the management of this disease, reducing dramatically the frequency of surgical intervention. Neurology has benefited greatly from modern diagnostic tools while psychiatry, though little has been learned about the cause of the major psychoses, has also benefited enormously by the development of drugs for the control of both schizophrenia and the depressive disorders and the emergence of cognitive-behaviour therapy and dynamic psychotherapy.

The second half of the 20th Century has also seen major progress in the diagnosis and management of cancer. Again this has followed from a combination of more sophisticated diagnostic technology combined with improvements in the techniques of radiotherapy and the development of powerful anti-cancer drugs on the part of the pharmaceutical industry. This approach has led to some remarkable improvements in the outlook for particular cancers, notably childhood leukaemia, and at least some forms of lymphoma. Progress towards the management of other cancers has been slower and reflects the results of more accurate staging and assessment of the extent and spread of the tumour; the management of many common cancers still remains unsatisfactory however. Similarly, although much progress has been made towards the prevention of common cancers, cervix and breast for example, by population screening programmes, the cost-effectiveness of screening for other common cancers, prostate for example, remains controversial.

There has also been a steady improvement in many aspects of maternal and child health. A better understanding of the physiology and disorders of pregnancy together with improved prenatal care and obstetric skills has led to a steady reduction in maternal mortality. In a developed country few children now die of childhood infection and the major pediatric problems are genetic and congenital disorders, which account for about 40% of admissions in paediatric wards, and behavioural problems. Until the advent of the molecular era little progress was made towards an understanding of the cause of these conditions. It is now known that a considerable proportion of cases of mental retardation result from definable

chromosomal abnormalities or monogenic diseases although at least 30% of cases remain unexplained. There have been major improvements in the surgical management of congenital malformation but only limited progress towards the treatment of genetic disease. And although a few factors such as parental age and folate deficiency have been incriminated, very little is known about the reasons for the occurrence of congenital abnormalities.

In summary, the development of scientific medical practice in the 20th Century has led to a much greater understanding of deranged physiology and hence has enabled many of the common killers of Western society to be controlled, though few to be cured. But while epidemiological studies of these conditions have defined a number of risk factors, and a great deal is understood about the pathophysiology of established disease, there is a major gap in our knowledge about how environmental factors actually cause these diseases at the cellular and molecular level. We will return to the question of how genomic technology may help to close this gap later in the chapter. Many of these issues are discussed more fully and with detailed references by Weatherall (1995).

**Consequences of the demographic and epidemiological transitions of the 20th Century**

*Demographic and epidemiological changes* The period of development of modern scientific medicine has been accompanied by major demographic change (Feachem *et al*, 1992; Chen 1996). The results of increasing urbanisation, war and political unrest, famine, massive population movements, and similar issues must have had a major effect on the health of communities during the 20th Century. On the other hand there has been a steady fall in childhood mortality throughout the New World, Europe, the Middle East, Indian subcontinent and many parts of Asia during this period, although unfortunately there has been much less progress in many parts of sub-Saharan Africa. Although much of this can be ascribed to improving public health and social conditions it seems likely that the advent of scientific medicine, particular the control of many infectious diseases of childhood, is playing an

increasingly important part in this epidemiological transition. And although surveys of the health of adults in the developing world carried out in the 1980's suggested that many of those between the ages of 20 and 50 years were still suffering largely from diseases of poverty, many countries have now gone through an epidemiological transition such that the global pattern of disease will change dramatically by 2020, with cardiorespiratory disease, depression, and accidents replacing communicable disease as their major health problems.

*New epidemics of non-communicable disease* While countries are undergoing the epidemiological transition they are increasingly caught between the two worlds of malnutrition and infectious disease on the one hand, and the diseases of developing countries, particularly cardiac disease, obesity and diabetes, on the other. This problem is exacerbated by the increasing epidemic of tobacco-related diseases in the developing countries.

The global epidemic of obesity and type 2 diabetes is a prime example of this type of problem (Alberti 2001). It is estimated that there are currently 150 million people affected with diabetes worldwide and that the number is expected to double by 2025. Furthermore it is associated with a greatly increased risk of cardiovascular disease and hypertension. Indeed, in some poorer countries the rate of stroke is already 4-5 times that in richer countries. These frightening figures raise the question as to whether, once developing countries have gone through the epidemiological transition, they may face the same pattern of diseases that are affecting the richer countries and that they may be much more frequent and difficult to control. And type 2 diabetes typifies the current state of modern scientific medicine; although much is understood about its deranged biochemistry, with the exception of its relationship to obesity very little is known about its cause.

*The problem of increasingly aged populations* Partly based on advances in scientific medicine the richer countries have to face another large drain on the health resources in the new millennium (Olshansky *et al*, 1990). In Great Britain for example, between 1981 and 1989 the number of people aged 75 to 84 rose by 16%,

and that of people aged 85 and over by 39%; the current population of males aged 85 or more is expected to reach nearly half a million by 2026, at which time there will be close on one million females in this age group. These figures reflect those for many of the richer countries and there will be a similar trend in every country that passes through the epidemiological transition. Although there are limited data about the quality of life of the aged, studies like the 1986 General Household Survey carried out in the United States indicated that restricted activity per year among people over the age of 65 years was 43 days in men and 53 days in women; these data say little about the loneliness and isolation of old-age. It is currently estimated that 20% of all people over the age of 80 will suffer from some degree of dementia, a loss of intellectual function sufficient to render it impossible for them to care for themselves. Again, scientific medicine in the 20$^{th}$ Century has provided highly effective technology for partially correcting the diseases of ageing while, at the same time, there has been very little progress towards understanding the biological basis of the ageing process. Furthermore, the problems of ageing and its effect on health care has received very little attention from the international public health community; these problems are not restricted to rich countries but are becoming increasingly important in middle-income and, to a lesser extent, in some low-income countries.

*Health and poverty in the era of scientific medicine* While it is self evident that dire poverty is one of the major causes of ill-health in the developing countries it should be emphasised that this phenomena is not confined to these populations. For example, in the UK, where healthcare is available to all through a government health service, there is a major discrepancy in morbidity and mortality between different social classes (Black 1980). Clearly this is not related to the accessibility of care, and more detailed analyses indicate that it cannot be ascribed wholly to different exposure to risk factors. Undoubtedly social strain, isolation, mild depression, and lack of social support play a role. However, the reasons for these important discrepancies, which occur in every developed country, remain unclear.

**Economic Consequences of High Technology Medicine**

It is self-evident that the current high technology medical practice based on modern scientific medicine must steadily increase the amount of expenditure on health. Regardless of the mechanisms for the provision of healthcare, its spiralling costs based on ever more sophisticated technology and the ability to control most chronic illnesses, combined with greater public awareness and demand for medical care, are resulting in a situation in which most of the richer countries are finding it impossible to control the costs of the provision of healthcare services.

The British National Health Service (NHS) offers an interesting example of the steady switch to high technology hospital practice since its inception 50 years ago (Webster 1998). Over that period its overall expenditure of health has increased fivefold, even though it absorbs a smaller proportion of the GDP than many of its European neighbours. At the start of the NHS there were 48,000 doctors in the UK; by 1995 there were 106,845, of whom 61,050 were in hospital practice and 34,594 in general (primary care) practice. Although the number of hospital beds halved over the first 50 years of the NHS, the throughput of the hospital service increased from three million to 10 million in-patients per year, at a time when the general population growth was only 19%. Similarly, there was a doubling of out-patient activity, and total attendances grew from 26 to 40 million. Since many developed countries do not have the kind of primary care referral programme which is traditional in the UK it seems likely that this large skew towards hospital medicine will be even greater.

The same trends are very clearly shown in countries like Malaysia which have been rapidly passing through the epidemiological transition and in which healthcare is based on a mixed public/private basis. In Malaysia, hospitalization rates have steadily increased since the 1970's, reflecting that utilization is slowly out-stripping population growth. This has been associated with a phenomenal rise, of more than 300 per cent, in the number of private hospitals and institutions. In 1996, the National Household Health Expenditure Survey showed that charges per day in private hospitals were 30 times higher than that in public hospitals. Undoubtedly

these figures reflect, at least in part, the acquisition of expensive medical technology which, in some cases has led to inefficient use of societal resources. For example, a survey at the end of the 1990's indicated that there were more MRI scanners in the Klang Valley than in all of Australia! Like many countries, the Malaysian government has now established a Health Technology Assessment Unit to provide a mechanism for the evaluation and cost-effectiveness of new technology. It also appears that privatisation has led to increased costs of pharmaceuticals and medical supplies in Malaysia. In 1944 the Government Medical Stores were privatised; in 1997 a study found that prices had increased 3.3 times (weighted) after privatisation.

These brief examples of the impact of high technology practice against completely different backgrounds of the provision of healthcare reflect the emerging pattern of medical practice in the 20th Century. In particular, they emphasise how the rapid developments in high-technology medical practice, and the huge costs that have accrued, may have dwarfed expenditure on preventive medicine, certainly in some rich countries and those that have gone through the epidemiological transition.

A central question for medical research and healthcare planning is whether the reduction in exposure to risk factors that is the current top priority for the control of common diseases, both in developed and developing countries, will have a major impact on this continuing rise of high-technology hospital medical practice. The potentials of this approach have been discussed in detail recently (WHO, 2002b). While the claims for the benefits of reducing either single or multiple risk factors are impressive there is no way of knowing to what extent they are attainable. Furthermore, if, as seems likely, they will reduce morbidity and mortality in middle-life, what of later? The WHO Report admits that it has ignored the problem of competing risks i.e. somebody saved from a stroke in 2001 is then 'available' to die from other diseases in ensuing years. And of course there is solid information about the role of risk factors only for a limited number of non-communicable diseases; very little is known about musculo-skeletal disease, the major psychoses, dementia, and many other major causes of morbidity and mortality.

The problems of healthcare systems and improving performance in healthcare delivery have been reviewed in a recent Report (WHO, 2000). Relating different systems of healthcare to outcomes is extremely complex but this report, if nothing else, emphasises the critical importance of research directed at healthcare delivery. As a response to the spiralling costs of healthcare many governments are introducing major reforms of their healthcare programs without pilot studies or any other scientific indication for their likely success. This vital area of medical research has tended to be neglected in many countries over the later years of the 20th Century.

**Summary of the Role of Scientific Medicine in the 20th Century**

The two major achievements of scientific medicine in the 20th Century, that is the development of clinical epidemiology and the partial control of infectious disease, have made only a limited contribution to the health of the developing countries. Although in part this is simply a reflection of their poverty and dysfunctional healthcare systems, and hence their inability to take advantage of the vaccines and other methods which have been evolved to control infectious disease, this is not the whole story. As exemplified by the fact that of 1233 new drugs that were marketed between 1975 and 1999, only 13 were approved specifically for tropical diseases, the problem goes much deeper, reflecting neglect of the specific medical problems of the developing countries on the part of the developed countries.

For those countries which have gone through the epidemiological transition and for developed countries the central problem is quite different. While the application of public health measures for the control of risk factors appears to have made a major impact on the frequency of some of their major killers, coronary artery disease and lung cancer for example, these gains have been balanced by an increase in the frequency of other common chronic diseases and the problems of an increasingly elderly population. At the same time remarkable developments in scientific medicine have allowed them to develop an increasingly effective high technology, patch-up form of medical practice. None of these countries have worked out a way of

controlling the spiralling costs of healthcare and, because of their increasing aged populations, there is little sign that things will improve. While there is considerable evidence that at least some of the diseases which produce this enormous burden on society may be at least partially preventable by the more effective control of risk factors, it is not clear to what extent this will be achievable and, for many diseases, these factors have not been identified. In short, scientific medicine in the 20th Century, for all its successes, has left a major gap in the understanding of the pathogenesis of disease between the action of environmental risk factors and the basic disease processes which follow from exposure to them, and which produce the now well-defined deranged physiology which characterizes them.

These problems are reflected, at least in some countries, by increasing public disillusion with conventional medical practice. This undoubtedly has its roots in the belief that if modern medicine could control infectious disease it would be equally effective in managing the more chronic diseases that took its place. When this did not happen, and when a mood of increasing frustration about what medicine could achieve had developed, there was a natural move towards trying to find an alternative answer to these problems. Hence in many countries there has been a major migration towards complementary medicine.

It is against this rather uncertain background that the role of science and technology for medical care in the future has to be examined.

## SCIENCE, TECHNOLOGY AND MEDICINE IN THE FUTURE

### Priorities for Biomedical Research in the Future

In setting the priorities for biomedical research in the future the central objective must be to restore the balance of research between rich and poor countries such that a far greater proportion is directed at the needs of the developing countries. In the 1990's it was estimated that even though 85% of the global burden of disability and premature mortality occurs in the developing world, less than 4% of global research funding was devoted to communicable, maternal, perinatal and nutritional

disorders that constitute the major burden of disease in developing countries (Global Forum for Health Research, 2002).

The second priority, given the current uncertainties about the timescale which will be involved in translating some of the remarkable advances of modern biology into clinical practice, is to analyse in much more detail methods of delivery of those aspects of healthcare which have already been shown to be both clinically effective and cost effective. It is vital that the delivery of healthcare is based on well-designed evidence-based pilot studies rather than current fashion or political guesswork. It is also essential to understand why there are such wide discrepancies in morbidity and mortality between different socio-economic groups in many of the developed countries and to define the most effective approaches to public education about the whole concept of risk and what is meant by *risk factors*. In addition, a great deal more work is required on mechanisms for assessing overall performance of healthcare systems.

The third priority must be to focus research on the important diseases which the biomedical sciences failed to control during the 20th Century. These include common communicable diseases like malaria, AIDS and tuberculosis, cardiovascular disease, many forms of cancer, all varieties of diabetes, musculo-skeletal disease, the major psychoses, and the dementias. Of equal importance is a better understanding of both the biology and pathophysiology of ageing together with trying to define its social and cultural aspects.

In the fields of child and maternal health the requirements for research differ widely in the developed and developing countries. In the developed countries there is a major need for more work on the mechanisms of congenital malformation and for the better control and treatment of monogenic disease. In addition, since scientific medicine in its broadest sense left the whole question of behavioural disorders of childhood in a state of increasing uncertainty in the 20th Century, this important problem needs more research. In the developing countries both child and maternal health pose different problems, mainly relating to the control of communicable

disease, nutrition, and basic education. But in many developing countries some of the common monogenic diseases, notably the haemoglobin disorders, also require urgent attention.

Many of these problems are of such complexity that they will only be solved by the unification of public health, epidemiology, the basic biological sciences, clinical research, and the social sciences.

In the sections that follow we will briefly outline some examples of the new technologies which should help to drive these new amalgamations forward.

**New Technologies**

*Genomics, proteomics and cell biology* Without doubt the fields of molecular biology and recombinant DNA technology were the major developments in the biological sciences in the second half of the 20$^{th}$ Century. The announcement of the partial completion of the human genome project in 2001 was accompanied by claims that knowledge gained from this field would revolutionise medical practice over the next 20 years. While after further reflection some doubts have been raised about this claim, not in the least the timescale involved, there is still considerable reason for optimism. For although it is clear that the majority of common diseases do not result from the dysfunction of a single gene, most diseases can ultimately be defined at the biochemical level; since genes regulate an organisms' biochemical pathways, their study must ultimately tell us a great deal about pathological mechanisms.

The genome project is not restricted to the human genome but encompasses many infectious agents, animals that are extremely valuable models of human disease, disease vectors, and a wide variety of plants. But obtaining the complete nucleotide sequence of an organism is one thing; working out the regulation and function of all the genes that it contains and how they interact with each other at the level of cells and complete organisms presents a much greater challenge. Indeed, these are questions which may take the rest of this century to clarify. But along the way there is very likely to be a valuable fall-out from this field for a wide variety of medical

applications. Many of these are outlined in a recent WHO Report (*Genomics and World Health* 2002).

The first applications of DNA technology in clinical practice were for isolating the genes for monogenic diseases. Either by using the candidate gene approach, or by utilising DNA markers for linkage studies, it has been possible to define the genes for many monogenic diseases. This information is being used in clinical practice for carrier detection, prenatal diagnosis, and for defining the mechanisms of phenotypic variability. It has been particularly successful in the case of the commonest monogenic diseases, the inherited disorders of haemoglobin, which affect hundreds of thousands of children in the developing countries (Weatherall and Clegg, 2001a,b). Through North/South collaborations it has been possible to set up screening and prenatal diagnosis programmes for these conditions in many countries, resulting in a marked decline in their frequency, particularly in Mediterranean populations (Box 1). Gene therapy, that is the specific correction of monogenic diseases, has been fraught with difficulties but these are slowly being overcome and it seems likely that this approach will be successful for at least some genetic diseases in the future.

From the global perspective one of the most exciting prospects for the medical applications of DNA technology is in the field of communicable disease. Remarkable progress has been made in sequencing the genomes of bacteria, viruses, and other infective agents and it will not be long before the genome sequence of most of the major infectious agents is available. Information obtained in this way should provide opportunities for the development of new forms of chemotherapy (Joët *et al*, 2003) and will be a major aid to vaccine development (Letvin *et al*, 2001). In the latter case DNA technology will be combined with studies of the basic immune mechanisms involved in individual infections in an attempt to find the most effective and economic approach to vaccine production. Recombinant DNA technology was used some years ago to produce pure antigens of hepatitis B in other organisms for the development of safe vaccines. More recently, and with knowledge obtained from the

various genome projects, interest has centred on the utility of DNA itself as a vaccine antigen. This was based on the chance observation that the direct injection of DNA into mammalian cells could induce them to manufacture, that is express, the protein encoded by a particular gene that had been injected. Early experiences of this approach have been disappointing but a variety of techniques are being developed to improve the antigens of potential DNA-based vaccines.

The clinical applications of genomics for the control of communicable disease are not restricted to infective agents. Recently, the mosquito genome has been sequenced, leading to the notion that it may be possible to genetically engineer disease vectors so as to make them unable to transmit particular organisms (Land, 2003). And a great deal is being learnt about genetic resistance to particular infections in human beings (Weatherall and Clegg, 2002), information that will become increasingly important when potential vaccines go to trial in particular populations.

The other extremely important application of DNA technology for the control of communicable disease, and one of particular importance to the developing countries, is its increasing place in diagnostics. The genomes of many bacteria and viruses have now been sequenced and rapid diagnostic methods have been developed based on the polymerase chain reaction (PCR) technique. These approaches have been further refined towards identifying organisms that exhibit drug resistance and also to sub-typing many classes of bacteria and viruses. Although much remains to be learnt about the cost-effectiveness of these agents compared with more conventional diagnostic procedures some promising results have already been obtained, particularly for identification of organisms that are difficult to grow or when a very early diagnosis is required (Harris and Tanner, 2000). This type of technology is being widely applied for the identification of new organisms and is gaining a place in monitoring vaccine trials (Felger et al., 2003). The remarkable speed in which it was possible to identify a new corona virus and its different sub-types as the causative agent of SARS and the way this information could be applied

to tracing the putative origins of the infection are a remarkable testament to the extraordinary value of research in this field (Ruan et al. 2003).

The fruits of genomics are likely to play an increasingly important role in the control and management of cancer (Livingston and Shivdasani, 2001). It is now well established that malignant transformation of cell populations results from mutations in two main classes of genes. First, oncogenes, genes which are involved in the major regulatory processes whereby cells interact with one another, respond to environmental signals, regulate how and when they will divide, and with many other intricate processes of cell biology. Second, there are the so-called tumour suppression genes; loss of function by mutation may lead to a neoplastic phenotype. In the rare familial cancers individuals are born with one defective gene of this type, but in the vast majority of cases cancer seems to result from the acquisition during our lifetime of one or more mutations of oncogenes. For example, in the case of the common colon cancers perhaps up to six different mutations are required to produce a metastasising tumour.

By using array technology, which allows scientists to examine the pattern of expression of many different genes at the same time, it is apparent that this varies greatly from tumour to tumour. This information is already providing valuable prognostic data for cancers of the breast, blood and lymphatic system. There seems little doubt that this type of approach will become an integral part of diagnostic pathology in the future and that genomic approaches to the early diagnosis of cancer and for identifying high risk individuals will become part of clinical practice. There is also preliminary evidence that it may be possible to interfere with the function or products of oncogenes as a more direct approach to the treatment of cancer, although early experience indicates that drug resistance due to mutation may be a problem with this form of therapy, as it is in more conventional forms of cancer therapy.

Although the general principle that most cancers results from the acquisition of a number of mutations involving oncogenes or tumor suppressor genes is widely

accepted, recently it has become clear that the situation may be much more complex. For example many tumors, apparently early in their evolution, show major chromosomal disruptions, often with the loss of entire chromosomes. What causes this chromosomal instability and its relationship to the acquisition of oncogene mutations remains to be worked out. But it is possible that cancer research in the near future will change its emphasis from attempting to find agents to interfere with the action of normal oncogene function towards trying to prevent whatever it is that causes the marked instability of the genetic make-up of a cell early in the development of cancer.

The genomic approach to the study of common diseases of middle life, coronary artery disease, hypertension, diabetes, and the major psychoses, for example, has been widely publicized (Collins and McKusick, 2001). Except in rare cases none of these conditions are due to a defective single gene but, rather, they appear to be the result of multiple environmental factors combined with variation in individual susceptibility due to the action of several different genes. The hope is that if these susceptibility gene(s) can be identified, an analysis of their products will lead to a better understanding of the pathology of these diseases, and offer the possibility of producing more definitive therapeutic agents. Better still, this approach may provide the opportunity to focus public health measures for prevention on genetically-defined subsets of populations.

So far there have been far more disappointments than successes in this approach. This is not surprising considering the complexity of these diseases, reflecting as it does the action of multiple and changing environmental factors, the small contribution of many different genes, and the ill-understood biological effects of ageing. Despite the enormous amount of funding that has been put into this endeavour it may well take a long time for these studies to come to fruition and any concept of ‘genetic medicine’ of this type must be viewed with caution; certainly it is unlikely to become a major part of clinical practice within the 10 to 20 years.

Pharmacogenomics is another potential development from the genomics revolution (Bumol and Watanabe, 2001). In this case the idea is that there is enormous individual variability in the metabolism of drugs and hence clinical medicine will move towards a stage when every person's genetic profile for the metabolism of common drugs will be worked out and become part of their physicians' armamentarium. At the same time, information of this type will be of considerable value to the pharmaceutical industry for designing more effective and safer therapeutic agents. Again, a word of caution is necessary. Although there are well-defined genetic polymorphisms that are responsible for unwanted side effects of drugs, this information is still rarely used in clinical practice. Furthermore, the plasma levels after the administration of most common drugs follow a normal distribution, indicating that if there is genetic variation, a number of different genes must be involved. Hence, while the idea of every person having their genetic profile for handling drugs as part of their standard medical care will take a very long time to achieve, if it ever happens, there is no doubt that this field will gradually impinge on medical research and clinical practice. For example, there is already evidence that genetic polymorphisms involved in the metabolism of drugs commonly used for the control of AIDS in Africa may play an important role in individual patients' response to therapy. Undoubtedly more examples will appear, but it remains to be demonstrated that it will be cost effective to analyse large populations for these polymorphisms as part of disease control programmes.

There are many other potential applications of genomic research for medical practice. Although somatic-cell gene therapy, that is the correction of genetic diseases by direct attack on the defective gene, has gone through long periods of slow progress and many set backs, the signs are that it will be successful for at least a limited number of monogenic diseases in the long term (Kaji and Leiden, 2001). This type of approach is likely also to play a role for shorter-term objectives and is already starting to have a place in the management of coronary artery disease and some forms of cancer. No doubt many other applications will be defined in the

future. DNA technology has already revolutionised forensic medicine and will play an increasingly important role in this field. Although it is too early to assess how much its application to the studies of the biology of ageing will produce information of clinical value, considering the massive problem of our ageing populations and the undoubted contribution of the ageing process to their illnesses, it is vital that work in this field expands. And although current work in the field of evolution using DNA technology seems a long way from clinical practice, it has considerable possibilities for helping us to understand the lack of adaptation of present-day communities to the new environments that they have created.

**Stem cell and organ therapy**

Stem cell therapy, or, to give its more popular if entirely inappropriate title, therapeutic cloning, is an area of research in cellular biology which is raising great expectations while, at the same time, some bitter controversies. It is not surprising that this field has caused so much excitement; transplant surgery has its limitations and the possibility of a ready supply of cells to replace diseased tissues, even parts of the brain, is particularly exciting. Stem cells can be obtained from early embryos, some adult and fetal tissues, and, at least theoretically, from other adult cells. Embryonic stem cells, which retain the greatest plasticity, are present at an early stage of the developing embryo, from about the $4^{th}$ to the $7^{th}$ day after fertilisation. Although there has been some progress in persuading them to produce specific cell types, much of the potential for this field so far has come from similar studies of mouse embryonic stem cells. For example they have been transplanted into mice with a similar condition to human Parkinson's disease, with some therapeutic success, and have also been used to try to restore neural function after spinal cord injuries.

There are, of course, other sources of stem cells. Many adult tissues retain stem cell populations. Bone marrow has been applied to the treatment of a wide range of blood diseases and it is clear that human marrow contains stem cells capable of

differentiating into the full complement of cell types found in the blood. There is preliminary evidence that they can also differentiate into other cell types given the appropriate environment; they may, for example be a source of heart muscle or blood vessel cell populations, but although stem cells have also been found in brain, muscle, skin, and other organs in the mouse, research into characterising similar cell populations from humans is still at a very early age. One of the major obstacles to stem cell therapy with cells derived from embryos or adult sources is that, unless they come from a compatible donor, they may be treated as "foreign" and rejected by a patient's immune system. Thus much research is directed at trying to transfer cell nuclei from adult sources into an egg from which the nucleus has been removed, after which the newly created "embryo" would be used as a source of embryonic stem cells for regenerative therapy for the particular donor of the adult cells. Because this technique, called somatic cell nuclear transfer, follows similar lines to those that would be required for human reproductive cloning this field has raised a number of controversies. Because much work needs to be carried out on human embryonic stem cells to learn more about the regulation of differentiation of cells of this type, this also has raised major ethical issues.

If some of the formidable technical problems of this field can be overcome, and, even more importantly, if different societies are able to come to terms with the ethical issues involved in this work, this field holds considerable promise for correction of a number of different intractable human diseases, particularly those involving the nervous system. Some of these issues have been reviewed recently (Institute of Medicine, 2002).

**Information Technology**

The explosion in information technology has important implications for all forms of biomedical research, clinical practice and teaching. The admirable desire on the part of publicly-funded groups in the genomics field to make their data available to the scientific community at large is of enormous value for the medical application of

genomic research. This goal has been achieved by the triumvirate of public databases established in Europe, USA and Japan (European Bioinformatics Institute, GenBank and DNA Data Bank of Japan, respectively). The entire dataset is held in triplicate, and therefore securely, on three continents. The continued development of accessible databases of this type will be of inestimable value to scientists, both in the developed and developing countries. The continued expansion of electronic databases and methods of publication will be of equal value, particularly to scientists in the developing countries.

At a more clinical level the further development of approaches such as telepathology will also help to link scientists in the developed and developing countries, and the increasing availability of telemedicine education packages will also help to disseminate good practice. But even if these few examples of the huge potential of this field are to be realised there will have to be a major drive towards training and recruitment of young information-technology scientists, particularly in the developing countries.

**Minimally Invasive Diagnostics and Surgery; Changes in Hospital Practice**

Given the spiralling costs of hospital care in the developed countries, and the likelihood of similar problems for the developing countries in the future, it is important to review aspects of diagnostics and treatment which may help to reduce these costs in the future. Changes in clinical practice in the latter half of the 20$^{th}$ Century have already made some impact on this problem. As discussed earlier in the British National Health Service the numbers of hospital beds occupied daily halved between 1950 and 1990 despite the fact that the throughput of the service, after allowance for change of definition, increased from three million to 10 million in-patients per year. Remarkably, by 1996, of 11.3 million finished consultant episodes already 22% were single day cases. How can this trend be continued? One of the major areas which has already shown enormous potential is the development of minimally invasive and robotic surgery (Mack 2001). Advances in imaging, endoscopic technology and instrumentation have made it possible to convert many surgical procedures from an

open to an endoscopic route. Major advances using these procedures have followed for gall bladder surgery, the treatment of adhesions, the removal of fibroids, nephrectomy, and many minor paediatric urological procedures. The recent announcement of successful hip-replacement surgery using an endoscopic approach offers an outstanding example of its future potential. Although progress has been slower, there are a number of promising approaches for the use of these techniques in cardiac surgery and for their augmentation by the introduction of robotics into surgical practice.

These trends, and those in many other branches of medicine, will be greatly augmented by advances in biomedical imaging (Tempany and McNeil, 2001). There has already been major progress in the development of non-invasive diagnostic methods by the use of magnetic resonance imaging, computer tomography, positron imaging tomography and improved ultrasonography. And there are many promising new areas of research focus which are utilising developments in understanding cellular function at the molecular level which, aided by new information technology, offer great promise for the future. Image-guided therapy is developing rapidly and non-invasive treatment methods, such as focussed ultrasonography are showing considerable promise. Techniques such as positron emission tomography and magnetic resonance spectroscopy offer the possibility of the rapid diagnosis of tumours, the assessment of the distribution of new chemotherapeutic agents, and the identification of more specific chemotherapy and radiotherapy as well as responses to them.

**Biomedical Engineering, Organ and Tissue Replacement and Cell Therapy**

Technological advances in the second half of the 20$^{th}$ Century led to a number of important diagnostic procedures, including imaging, ultrasonics, the development of non-invasive pulse oximeters, implantable defibrillators, and many others (Griffith and Grodzinsky, 2001). At the same time organ replacement became routine in the case of they kidney, heart and cornea, and slow progress was made towards the concept of islet-cell transplant for the control of diabetes. With the potential fusion of

engineering technology with molecular and cell biology the discipline of bioengineering is likely to expand dramatically in the future. The remarkable pace of development of bio-micro-electromechanical systems together with the improvements in microlevel fluid pumping, mixing and reaction circuit systems are likely to give rise to a new era of chip diagnostics, enabling routine and sensitive analysis of thousands of molecules simultaneously from a single sample. Technology of this type, and increasing ability to incorporate molecular information into complex modelling, will undoubtedly lead to a revolution in the early detection of disease.

There will also be advances in developing selective immune tolerance, of major importance for transplantation biology (Niklason and Lenger, 2001). Recent work in the stem cell field has raised the potential for developing cell lines for individual tissues and organs. Although at the present time the most effective source for stem cells of this type is from human embryos it is believed that it will be possible to extend this facility to develop stem cells derived from adult tissues in the future. This approach, combined with the development of engineered tissues by using polymers with micro-architecture similar to native tissues, may revolutionise the fields of tissue repair and transplantation. There are, however, many uncertainties and this field may take a long time to evolve to a stage at which it is part of regular clinical practice.

**Human development, child and maternal health**

Among the major developments in molecular and cell biology in the future, a better understanding of the mechanisms of human development and the evolution of functions of the nervous system offer some of the most exciting prospects (Goldenberg and Jobe, 2001). In the long term this field may well have important implications for reproductive health and birth outcomes. The role of a better understanding of the monogenic causes of congenital malformation and mental retardation was mentioned earlier in this chapter. Already thoughts are turning to the possibility of the isolation and clinical use of factors that promote plasticity of brain

development, and specific modulators of lung, gut and brain are forecast to start to play an increasing role in obstetric practice. A better understanding of the mechanisms leading to vasoconstriction and vascular damage as a cause of pre-eclampsia has the potential for reducing the frequency and the better management of this common complication of pregnancy. Similarly an increasing appreciation of the different genetic and metabolic pathways which are involved in spontaneous pre-term births should lead to effective prevention and treatment, targeting specific components of these pathways and hence leading to reduction in the frequency of premature births. It is also believed that an increasing knowledge of the mode of action of different growth factors and promoters of gut function will enhance growth and development of pre-term infants. But, given the complexity of developmental biology, many of these advances may be far in the future.

**Neuro-psychiatry**

Particularly because it is predicted that depression and related psychiatric conditions will be a major cause of ill-health by 2020, and because of the increasing problem of dementia in the elderly, this field will be of increasing importance in the future (Cowen and Kandell, 2001). There is already clear evidence that developments in the basic biomedical sciences should play a major role in the better diagnosis and management of these disorders. Furthermore, the application of new technologies promises to lead to increasing co-operation between neurology and psychiatry, especially for the treatment of illnesses such as mental retardation, and cognitive disorders associated with Alzheimer and Parkinson diseases that clearly overlap the two disciplines.

The remarkable developments in imaging technology, many of which are applicable to neuro-psychiatric disease, were discussed earlier in this chapter. The increasing application of functional imaging, together with a better understanding of biochemical function in the brain is likely to lead to major advances in our understanding of many neuro-psychiatric disorders and hence provide opportunities for their better management. Early experience with fetally-derived dopaminergic neurons to treat

parkinsonism has already proved to be successful in some patients and has raised the possibility that genetically manipulated stem cell treatment for this and other chronic neurological disorders may become a reality. Promising methods are being developed for limiting brain damage after stroke and there is increasing optimism in the field of neuronal repair based on the identification of brain-derived neuronotrophic growth factors.

There is very strong evidence for a major genetic component to the common psychotic illnesses, notably bi-polar depression and schizophrenia. Many studies are already being directed at total genome searches for some of the genes involved, and although progress has been slow there are reasonable expectations for success in this very important endeavour. If some of these genes can be identified they should provide targets for completely new approaches to the management of these diseases by the pharmaceutical industry. Recent successes in discovering the genes involved in such critical functions as speech indicate the extraordinary potential of this field. Similarly, lessons learnt from the identification of the several genes involved in familial forms of early-onset Alzheimer's disease have provided invaluable information about some of the pathophysiological mechanisms involved, work which is having a major impact on studies directed at the pathophysiology and management of the much commoner forms of the disease which occur with increasing frequency in aged populations.

In short, the neurosciences promise to be the most exciting field for development in the biological sciences in the new millennium. While the clinical applications may be slower to follow, enough information has been obtained over recent years to suggest that they will undoubtedly come to fruition.

**Nutrition and Genetically Modified Crops**

Over the next 25 years, the world's population is likely to increase by approximately 2.5 billion people, with much of this projected growth occurring in developing countries. Consequently, food requirements are expected to double by 2025. On

the other hand, there has been a decline in the annual rate of increase in cereal production; the present yield is well below the rate of population increase. It has been estimated that about 40% of planned productivity in parts of Africa and Asia, and about 20% in the developed world, is lost to pathogens.

Based on these considerations there is no doubt that the genetic modification (GM) of plants has considerable potential for improving the world's food supplies and hence the health of its communities. The main aims of GM plant technologies are to enhance the nutritional value of crop species and to confer resistance to pathogens. There have already been several successes in GM technology in both these objectives.

There is still considerable controversy about the relative effectiveness of GM crops as compared with those which are produced by conventional means, particularly with respect to economical issues of farming in the developing world. And there are still concerns about the safety of GM crops, and a great deal more research is required in this field. The results of recent bio-safety trials in Europe raise some concerns about its effects on biodiversity (Giles, 2003).

It should be remembered however that plant genetics has more direct potential for the control of disease in humans. By genetically modifying plants it is hoped it will be possible to produce molecules toxic to disease-carrying insects and edible vaccines which are cheaper than conventional vaccines and which can be grown or freeze dried and shipped anywhere in the world. A promising example is the production of hepatitis B surface antigen in transgenic plants for oral immunization. Work is also well advanced for the production of other vaccines by this approach.

These issues are considered further in the report *Genomics and World Health* (WHO, 2002).

**Integration of the Medical Sciences; Organisational Priorities for the Future**

From these brief examples of the likely direction of biomedical research in the future some tentative conclusions can be drawn about its likely effects on the pattern of global health care.

From the viewpoint of global health, the control of communicable disease will remain the top priority. Whilst this can be achieved in part by improving nutrition and sanitation, and the application of related public health measures in the developing countries, the search for vaccines or better chemotherapeutic agents must also remain a high priority. However, although the grounds for optimism that new vaccines will become available are well founded, there are still many uncertainties, particularly in the case of biologically complex diseases like malaria. For this reason it is vital that a balance is struck between the basic biomedical science approach and the continued application of methods to control these diseases by more conventional and well-tried methods.

For the bulk of the common non-communicable diseases the situation is even less clear. While it seems certain that much more humane, cost-effective and clinically effective approaches to their management will be developed, mainly by high technology and expensive procedures, the position regarding prevention and a definitive cure is much less certain. Hence, it is clear that the programme for reducing risk factors, as outlined in *The World Health Report, 2002* (WHO, 2002b ) should be followed. However, there is a strong case for an amalgamation of the public health, epidemiological and genomic sciences to evolve pilot studies to define whether it will be both cost-effective and more efficient to focus these programmes on high-risk subsets of populations. And for those many chronic diseases for which no risk factors have been defined, strategies of the same type should be established to try to define potential environmental factors which may be involved. Although there may be surprises along the way, like the discovery of the infective basis for peptic ulceration, the multilayered environmental and genetic complexity of these diseases combined with the ill-understood effects of ageing suggests that there will

be no quick or easy answers to these problems; future planning for global health services must take this into consideration.

Given these uncertainties, there is an important place for the involvement and integration of the social sciences and health economics into future planning for biomedical research. There are major gaps in knowledge about public perceptions and understanding of risk factors, lack of information about the social and medical problems of ageing populations, and widespread uncertainty about the most cost-effective and efficient ways of administering healthcare, both in developing countries and in those that have gone through the epidemiological transition and which already have advanced healthcare systems.

In short, the picture which is emerging is that there are reasonable grounds for optimism that better and more definitive ways of preventing or curing communicable diseases will gradually become available; it is only the timescale that is uncertain. But for the bulk of non-communicable diseases, while there is no doubt that there will be major improvements in management based on extensive and increasingly high technology practice, the outlook for their prevention and definitive cure is much less certain. Hence, it is vital that research in the basic biomedical sciences is directed both at their cause and prevention, and that work in the fields of public health and epidemiology continues to be directed towards better utilization of what is known already about their prevention and management in a more cost-effective and efficient manner.

**Priorities for the Developing Countries**

The role of genomics and related high technology research and practice in the developing countries has been discussed in detail in a recent WHO Report (*Genomics and World Health*, WHO 2002). The central question which was addressed was, given the current economic, social and healthcare problems of the developing countries, is it too early to be applying the rather limited clinical applications of genomic and related technology into their healthcare programmes?

The report concluded that it is not too early, and subsequent discussion has suggested that this decision was right; where DNA technology has already been proven to be of cost-effective value it should be introduced as soon as possible (Weatherall, 2003). Particular examples include the common inherited disorders of haemoglobin (see Inherited Disorders of Hemoglobin, Chapter X) and, in particular, the use of DNA diagnostics in the field of communicable disease. The advantage of this approach is that it provides a technical base on which further applications of this field can be built as they become available. It also provides the impetus to develop the training required, initiation of discussions on the many ethical issues which work of this type may involve, and the establishment of the appropriate regulatory bodies. The way in which this type of programme should be organised through North/South collaboration, local networking, and related structures, monitored by the WHO, were clearly defined in the report.

But for the full fruits of genomics to be made available to the developing countries, and for these advances not to widen the gap in healthcare provision between North and South, the most pressing and potentially exciting developments from the new technologies of science and medicine will have to be exploited by scientific research in the developed countries. This is particularly pressing in the case of the major communicable killers, malaria, tuberculosis and AIDS. Similarly, and equally important, if the developing countries are to make the best use of this new technology for their own particular disease problems, there will have to be the establishment of partnerships between both academia and the pharmaceutical industries of the North and South.

In short, it is very important that work starts now in applying the advances which are stemming from the basic biological sciences for the health of the developing world. This will form a platform on which future advances can be integrated into healthcare programmes for these countries. But because of uncertainties of the timescale involved it is vital that more conventional public health approaches to medical care

are not neglected and that a balance is struck between research in this area with that in the emerging biomedical sciences.

**Economic Issues for future medical research**

The central economic issues regarding medical research in the future are how it is to be financed and how its fruits are to be used in a most cost-effective way in both developed and developing countries. Currently, it is carried out both in the private and public sectors. Work in the private sector is based mainly in the pharmaceutical industry and, increasingly, in the many large biotechnology companies which have evolved rapidly over recent years following the genomic revolution. In the public sector the major sites of research are the universities, government research institutes, and centers either within the universities or free-standing which are funded through a variety of philanthropic sources. The input of the latter varies greatly between countries; in the UK the Wellcome Trust provides a proportion of funding for clinical and basic biomedical research which approaches that of the government, and in the USA the Howard Hughes organization also plays a major though proportionally less important role in supporting medical research. Similarly, the Bill and Melinda Gates Foundation, and other large international philanthropic foundations, are contributing a significant amount of funding for medical research.

As exemplified by the Report of the WHO Commission on Macro-Economics and Health (2001) there is considerable discussion about how to mobilize skills and resources of the richer countries for the benefit of the health of the developing world. However, it is still far from clear how this international effort should be organized, or, even more importantly, funded. A number of models have been proposed including the creation of a new global institute for health research and a global fund for health research with an independent, streamlined secretariat analogous to the Global Fund to Fight AIDS, Tuberculosis and Malaria. Recently, a number of large donations have been given, either from governments or from philanthropic bodies to tackle some of the major health problems of the developing world. While many of these approaches are admirable, particularly those which involve single donations raise

the critical problem of sustainability. Those with experience in developing interactions between the North and South will have no doubts about the long periods of sustained work that is often required for a successful outcome.

Based on uncertainties about sustainability and the efficiency of large international bodies, it has been suggested that a virtual global network for health research be established in which the leading research agencies of the North and South take part, together with a co-ordinating council (Keusch and Medlin, 2003). In this scheme or in a modified form (Pang, 2003), both government funding agencies and philanthropic bodies would retain their autonomy and mechanisms of funding while, at the same time, their individual programs would be better integrated towards the problems of global health.

A central problem of both these private and public patterns of funding for medical research is that hitherto the rich countries have tended to focus their research on their own diseases and have, with a few exceptions, tended to ignore the broader problems of the developing countries, a trend which has resulted in the well-known 10/90 gap in which over 90% of the worlds expenditure on health research is directed at diseases which, numerically, affect a relatively small proportion of the world's population. If the enormous potential of modern biomedical research is not to result in a widening of the gap in healthcare between North and South it is vital that this situation is corrected. The governments of the richer countries may be able to encourage a more global view of research activity on the part of their pharmaceutical and biotechnology industries by various tax advantages and other mutually beneficial approaches. It seems likely that progress in this direction will be slow however. For this reason there are many attractions about moving quickly towards a virtual global network for research, bringing together the research agencies of the North and South. Although those of the North that rely on government and charitable funding may find it equally difficult to convince their governments that more of their budget should be spent on work in the developing world, it is vital that they move in this direction, possibly by directing at least some

proportion of their overseas aid to this highly effective approach to developing North/South partnerships.

In short, to produce the funding required for medical research in the future, and to ensure that it takes on a much more global view of its objectives, there will have to be a complete change in attitude on the part of the developed countries. This, in turn, will require a similar change of attitude on the part of those who educate doctors and medical scientists, with a much more global perspective of disease. The introduction of considerable sums of research monies into the international scene by governments or philanthropic bodies as single, large donations, while very welcome, will not form the basis for the kind of sustainable research programme that is required. Rather, the attitudes of both government funding agencies and charitable bodies in the richer countries will have to change, with a greater proportion of their funding being directed at diseases of the developing world in the future. To achieve this end will require a major programme of education into the global problems of disease at every level, including governments, industry, and universities, charitable organizations and every other body that is involved in the medical research endeavour.

**Education**

The central theme of the previous sections is that the potential fruits of the exciting developments in the biomedical sciences will only be achieved if there is a complete change in attitude on the part of the developed countries, with the evolution of a much more global attitude to the problems of medical research and health care. This will have to start in the universities of the richer countries, with much more global perspective in medical education such that the next generation of young people are more motivated towards developing research careers which take a much more international view of the problems of medical research. There are already excellent examples of the value of the development of North/South partnerships between universities and other academic institutions. If this trend is pursued, it could have a major effect on disseminating the fruits of medical research in the future. But

this will require a major change of emphasis in education and will be difficult to achieve unless those who control the university education and research programs can be convinced that funding is available for further development in these new directions (Weatherall 2003).

As outlined in the previous sections, an effective approach to increasing global funding for internationally based research is through virtual global networks involving the leading research agencies in the North and South. Hence there will have to be a similar effort towards education of these agencies and their governments that this is a cost-effective approach to improving the level of health globally. In particular, it will be vital to persuade them that this may be an effective use of their programs of aid for the developing countries. To achieve this it may be necessary to carry out a number of pilot studies showing the economic value of North-South partnerships in specific areas of medical research. Indeed, there has been experience of a number of these partnerships already in several countries and information of this type almost certainly exists. Some examples are shown in Boxes 1 and 2.

There are, of course, much broader issues involving education which will be required in the future for the better exploitation of medical research. The problems of public education required for the developing countries to partake in the fruits of the genome revolution were set out in detail in a recent WHO Report (*Genomics and World Health,* 2002). But a great deal of work along these lines is also required for the developed countries. There is a growing suspicion of modern biological science and of modern high-technology medicine, a factor which is probably playing a role in driving many communities in the developed countries towards complementary medicine. These trends undoubtedly reflect the inadequacy of science education in schools and the resulting lack of scientific literacy in both the general public and their governments. If trust is to be restored between the biomedical sciences and the public a great deal of effort will have to be made to improve the level of scientific literacy together with the development of a much more open dialogue between scientists and the community about what modern science is trying to achieve. This

will be increasingly important as the work on the basic biomedical sciences impinges on areas such as gene therapy, stem cell research, and the collection of large DNA databases to be used for both research and therapeutic purposes in the future.

The difficulties in achieving a more global view of medical research and healthcare on the part of the developed countries for the future should not be underestimated. But without a major effort along these lines it seems certain that the undoubted potential of the modern biomedical sciences will simply widen the gap in healthcare between North and South.

**Ethical issues**

There are few advances in scientific medicine which have not raised new ethical issues for society. The genomics era has been particularly problematic in this respect and although many of the initial fears and concerns have been put to rest by sensible debate and the development of effective control bodies, new problems have continued to appear. Currently, the ill-named field of therapeutic cloning is still full of unresolved issues regarding human embryo research, the creation of embryos for research purposes, and several other uncertainties. But these questions should not be over-emphasised at a time when most societies face even more onerous ethical issues. For example, as the size of our aging population increases, many societies may have to face the extremely difficult problem of rationing of medical care. And the theme which is recurring throughout both rich and poor countries is how it will be possible to provide an adequate level of health care which is equally available to every income group. In many of the developed countries there is still a major discrepancy in the quality of health and survival times between rich and poor sectors of their communities.

These are extremely important issues and every country requires a completely independent bioethics council which can debate them uninhibited by pressures from government, commerce, or pressure groups of any kind. Indeed, our approaches to developing a more adequate ethical framework for much of medical decision making

is another neglected area which requires a research input from many different disciplines.

**Why do we need research?**

As we move into the new millennium it is important to appreciate that there is considerable public suspicion about both the activities and value of biomedical research. This is generated in part by its exaggerated claims over recent years, many of which have not come to fruition, an uneasy feeling that it is venturing into areas which would best be avoided, and a lack of understanding about the complexity of many of the problems that it is attempting to solve. At the same time, many government departments that run national health care programs, the private sector with the exception of the pharmaceutical industry, and many non-government organizations, set aside extremely small fractions of their overall expenditure for research. For many of these organizations, in which the stresses of the daily provision of programs of health care together with the crisis-management scenarios which have to follow rapid change or major failures in health care provision, research seems to be irrelevant.

One of the major challenges for the biomedical research community in the future, therefore, will be how better to educate the public about its activities and how to restore their faith and support for the medical research endeavour. At the same time it will be vital to educate many governments and non-government organizations about the vital importance of decision making based on scientifically-derived evidence. Medical care can only get more complex and expensive in the future; its problems will not be solved by short-term, politically driven activity. The need for good science, ranging from studies of molecules to communities, has never been greater.

**SUMMARY**

Research in basic human biology and the biomedical sciences is entering the most exciting phase of its development. However, it is very difficult to anticipate when the

fruits of this explosion in scientific knowledge will become available for the prevention and treatment of the major killers of mankind. Thus medical research in the future must strike a balance between the well-tried approaches of epidemiology and public health and clinical investigation at the bedside with the application of discoveries in the completely new fields of science that have arisen from the genome revolution. But if the fruits of this balanced approach towards the future provision of healthcare is not to continue to worsen the gap between North and South there will have to be a complete change of attitude towards healthcare research and practice on the part of the richer countries. This will require a major effort towards education in global health problems, involving international non-government organizations, governments, universities, and the private sector. Equally important, it will require a major change of emphasis in the universities of the developed countries towards education programs in science and medicine which provide medical scientists of the future with a much more global perspective of health and disease.

**Box 1**

**North/South partnerships for the control of the genetic disorders of hemoglobin**

In the early 1970's it became apparent that the inherited disorders of hemoglobin, notably the thalassemias, were becoming particularly common throughout many tropical countries, particularly those that had gone through the epidemiological transition. For example, in Cyprus (population 771,000) it was estimated that, if no steps were taken to control the disease, in about 40 years time the blood required to treat all the severely affected children would amount to 78,000 units per annum, 40% of the population would be donors, and the total cost to the health services would equal or exceed the island's health budget (WHO 1983). Over subsequent years it became apparent that the hemoglobinopathies would also place a major drain on health resources in many other regions, notably the Indian subcontinent and many of the countries of Southeast Asia. In the mid-1960's methods were developed to identify the defects in thalassemia in fetal blood samples obtained at about 18 weeks of pregnancy. By evolving partnerships between laboratories in the Mediterranean islands and those in the United Kingdom and the USA it was possible to develop methods for the prenatal detection of the serious forms of thalassemia. Similarly, when DNA diagnostics were developed for the different thalassemias, the same partnerships worked out the particular thalassemia mutations in different racial groups. During this process laboratory workers from the developing countries were trained in the techniques of DNA analysis and were able to return to their countries and set up prenatal diagnosis programs. These programs were sustained over long periods and resulted in a number of centers in the developing countries establishing central reference laboratories, screening programs and prenatal diagnosis.

At the same time extensive public education programmes were established to explain the nature of genetic disease in general, and thalassemia in particular. They were accompanied by the establishment of premarital heterozygote screening and

genetic counseling programs. Eventually, a high proportion of mothers who carried affected fetuses opted for termination of pregnancy.

These North/South partnerships led to a major decline in the frequency of new births of babies with severe thalassemia, particularly in the Mediterranean islands but also to a lesser extent in mainland populations. By the mid-1990's these programs had been set up in many countries in the developing world, all based on the same interactive North/South approaches (Cao et al, 1998; Weatherall and Clegg, 2001a). Since such data as exist indicate that population screening and counselling have little effect on marital choice or reproductive behaviour (see Weatherall and Clegg, 2001a), prenatal diagnosis programs of this kind, in populations in which they are acceptable, offer the most effective way of controlling common genetic disease, at least until curative therapy is available.

**Box 2**

**The Wellcome Trust-Oxford University Tropical Medicine Research Program**

In 1979 the United Kingdom Wellcome Trust, a large medical charity, developed an experimental program with Oxford University to determine whether it was possible to develop long-term, sustainable joint research programs between North and South. The first center was developed in Bangkok, Thailand; subsequent centers were established in Kilifi, Kenya and Ho Chi Minh City, Vietnam. The objective of these centers was to develop interactive programs whereby research workers from the UK could spend prolonged periods working overseas, young scientists from the UK could carry out research fellowships, and medical students could be introduced to the medical problems of the developing countries on short-term visits. At the same time, both long and short-term staff were recruited locally so that the teams would be genuinely interactive and young scientists from the developing country could spend periods of training in Oxford. Because the North partner was based in a University Medical School the programme could call on a broad range of scientific and clinical expertise on different aspects of its program.

This long-term program has allowed a number of scientists from the developing countries to obtain further training in Oxford, has encouraged many extremely able young medical scientists into careers in research relating to the developing countries and has produced a number of leaders in international health. It has also provided an excellent introduction to the health problems of the developing countries for many medical students. In particular it has been sustainable: the Bangkok center has now been active for 22 years.

Because of its base in a medical school it has also been possible to recruit short-term experts in a wide variety of fields for short-term visits to the units. This has been a major factor in their success in developing improved treatment protocols for malaria and many other communicable diseases, and, in particular, to apply the breadth of approach required for the successful elucidation of the complex

pathophysiology of many of these conditions. Furthermore, by linking these units with basic science institutes in Oxford it has been possible to carry out a broad spectrum of research ranging from the bedside to the molecular pathology of communicable diseases and playing an important role in the Malaria Genome project.

This program provides a useful model of how longterm, sustainable research programs can be established between the North and South, to their mutual benefit. Other models are described in *Genomics and World Health* (WHO, 2002).

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